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**Nuclear transfer nTreg model reveals fate-determining TCR-beta and novel peripheral nTreg precursors.**

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**Public Summary:**

To study the development and function of "natural-arising" T regulatory (nTreg) cells, we developed a novel nTreg model on pure nonobese diabetic background using epigenetic reprogramming via somatic cell nuclear transfer. On RAG1-deficient background, we found that monoclonal FoxP3+CD4+Treg cells developed in the thymus in the absence of other T cells. Adoptive transfer experiments revealed that the thymic niche is not a limiting factor in nTreg development. In addition, we showed that the T-cell receptor (TCR) beta-chain of our nTreg model was not only sufficient to bias T-cell development toward the CD4 lineage, but we also demonstrated that this TCR beta-chain was able to provide stronger TCR signals. This TCR-beta-driven mechanism would thus unify former per se contradicting hypotheses of TCR-dependent and -independent nTreg development. Strikingly, peripheral FoxP3-CD4+T cells expressing the same TCR as this somatic cell nuclear transfer nTreg model had a reduced capability to differentiate into Th1 cells but were poised to differentiate better into induced nTreg cells, both in vitro and in vivo, representing a novel peripheral precursor subset of nTreg cells to which we refer to as pre-nTreg cells.

**Scientific Abstract:**

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